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			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 11/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1 and 4-25 in the reply filed on 9/6/2005 is acknowledged. Claims 2 and 3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 1, 4-25 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1 and 4-25 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as it is dependent on a rejected claim and shares the same indefiniteness.

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1. Recitation of the phrase " and pharmaceutically acceptable salt, hydrate..... thereof" in claim 1, renders claim 1 and its dependent claims indefinite as it is not clear whether claim 1 is a compound claim or a composition claim with compound and its salts etc. Note Markush choices should be in alternate and singular form.

Furthermore, the proviso li in claim 1 is no longer applicable to the elected subject matter. Its deletion is suggested.

In addition claim 1 recites a prodrug thereof at two places which is confusing and unclear as to what is intended. Note the definition of R_3 includes a prodrug and the last line of the claim 1 recites the same.

Furthermore, recitation of N-protecting group in the definition of R_3 renders the claim indefinite as it is not clear what is a metes and bounds of the claim1. A nitrogen protecting group can be any number of groups with varying structural features and there is no evidence in the specification that they all will have the same intended use.

2. Claim 9 is indefinite as it appears to be missing a an "and" before the third species and for reciting " and their pharmacologically acceptable salts and solvates thereof. First of the choices of species should have the "and" before the last species. Secondly, as recited the claim relates to a composition of species and their salts and solvates. Note Markush recitation should be in alternate form and in singular. In addition, claim 9 is improper dependent claim as it recites a choice of "solvate" which is not recited in claim 1.

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3. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the actual reactants are omitted rendering the claim a cryptic claim. Not reacting with chemical reagents wouldn't lead to desired product.
4. Claim 25 lacks antecedent basis in claim 1 on which it is dependent.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrug of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability

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or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The direction concerning the prodrug is found in page 11 the passage spanning lines 3-7. There is no working example of a prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly

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relevant. Banker (Modem Pharmaceuticals) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. I) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 1 and 4-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts

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does not reasonably provide enablement for making solvate or hydrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof. (Note hydrate in claim 1 and solvate in claim 9) Specification is not adequately enabled as to how to make hydrate of compounds of formula (I) Specification has no example of hydrate of the instant compounds. Specification on page 33 recites solvate or hydrate thereof but there is no enabling of such compounds.

The compound of formula I embrace 2, 4-substituted-pyrimidine compounds substituted with variable groups R¹, R², R³ and R⁴.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in thousands of compounds. This

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is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any hydrate or solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to hydrates, which means a different solvent or even the moisture of the air that might change the stable region of the hydrate. In the instant case of hydrate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of hydrates in

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unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. The predictability or lack thereof in the art:

Hence, the solvate and hydrate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and hydrates. There is no example of a solvate or hydrate of instant compound. One hundred and twenty four compounds (including pyridine, pyrimidine and pyrazines) were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or hydrate and additional direction or guidance is needed to make them. Specification has no such direction or guidance.

4. The presence or absence of working examples:

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate or even hydrate. These cannot be simply willed into existence. As was stated

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in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the ‘881 patent do not produce the postulated compounds... there is ...‘ no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and hydrates of these compounds exist and therefore can be made.

5. The breadth of the claims & the quantity of experimentation needed:

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate and hydrate of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 11-13, 15-21 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of obesity embraced, does not reasonably provide enablement for prophylaxis of any or all diseases and disorder embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim 11 and its dependent claims 12-13, 15-21 and 23-24 are drawn to "for prophylaxis or treatment of serotonin-related medical condition".

Claims 11 and 23-24 are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification. In the instant case, because of the interaction of the compound formula I with serotonin receptor, it is recited that instant compounds are useful for prophylaxis and treatment of any or all medical conditions for which there is no adequate written description and enabling disclosure in the instant specification. The scope of the claims includes any or all medical condition due to serotonin receptor inhibition including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these

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claims includes treatment and prophylaxis of various medical conditions which are not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have serotonin receptor inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all medical conditions stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as serotonin receptor inhibitor that would be useful for all sorts of medical conditions. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of neurological diseases. are very difficult to treat or to prevent and despite the fact that there are many drugs with the same mode of action..

The scope of the claim includes prophylaxis of not only any or all conditions but also those condition yet to be discovered as mediated by serotonin for which there is no enabling disclosure.

The term “ prophylaxis” actually means to prevent spread of a disease (as per Meriam Webster’s Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the “prevention” effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

The scope of the claims involves thousands of compounds of claim 1 as well as the thousand of diseases embraced by the term medical condition

No compound has ever been found to treat and prevent all types of medical conditions generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Thus, it is beyond the skill of clinician today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001, wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method of prophylaxis solely based on the agonist activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See non-patent literature provided in the Information Disclosure Statement.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or

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lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Prophylactic and therapeutic use of the compounds in serotonin related medical condition that require 5-HT_{2c} agonist activity.

2) The state of the prior art: The publications cited in the Information Disclosure Statement expressed, at the time of the instant invention was made, that prophylaxis and treatment of medical conditions mediated by serotonin by 5-HT_{2c} agonist activity i is still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibiting 5-HT_{2c} activity are unpredictable and at best limited to treatment of obesity.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to 5-HT_{2c} activity.

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7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baroni et al. 0580465..

Maccoss et al. teaches several heterocyclyl piperazine compounds useful as %-HT3 agonists, which include instant compounds. See entire documents, especially page, formula I and note the definition of, X, Y, R, R₁ and R₂ overlap with instant variable groups. Note when R₂ is halogen, the compounds taught by Baroni et al. include instant compounds. Note the process of making is same as recited instant claim 22

See pages 4-5 for examples 1-3 which show a pyridine analog.

Instant claims require a pyrimidine core while Baroni et al exemplifies only pyridine core. However, Baroni et al clearly teaches equivalency of the exemplified pyridine compounds with those of pyrimidine compounds generically claimed for compound of formula I. See page 2 and note Y can be N and with X as CH.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted piperaziny-

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pyrimidines including those generically taught as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson whose telephone number is (571) 272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

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